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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/570,043	FUSSENEGGER ET AL.	
	Examiner	Art Unit	
	MARIA LEAVITT	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 April 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 and 9-27* is/are pending in the application.

4a) Of the above claim(s) *10-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant is advised that the prior office action filed on 06-09-2009 is vacated. The examiner called Applicants' attorney of record, William R Schmidt, to explain that the notice of non-compliant amendment (37 CFR 1.121) filed on 06-09-2009, in response to Applicants' amendment filed on 04-24-2009, was filed in error. In the notice of non-compliant amendment, the examiner contended that the text of amended claims 1-4 and 9 filed on 04-24-2009 was not submitted with markings to indicate the changes that have been made relative to the immediate prior version of claims 1-4 and 9 filed on 08-29-2008. This is not correct. The prior version of claims 1-4 and 9 was filed on 03-19-2009 and not 08-29-2008. The examiner inadvertently overlooked Applicants' amendment to the claims filed on 03-19-2009.

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 03-19-2009 has been entered.
2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
3. Claims 1-4 and 9-27 are pending. Claim 1 has been amended by Applicant's amendment filed on 04-24-2009. Claims 10-27 were previously withdrawn from consideration as being directed to non-elected invention pursuant to 37 CFR1.14(b), there being no

allowable generic or linking claim. Because applicant did not distinctly and specifically pointed out the supposed errors in the restriction requirement, the election was previously treated as an election **without traverse** (MPEP § 818.03(a)).

4. Accordingly, claims 1-4 and 9 are currently under examination to which the following grounds of rejection are applicable.

Withdrawn Rejections in response to Applicants' arguments or amendments

35 USC § 112- First paragraph- Written description

In view of Applicants' amendment of claim 1 to specifically claim the Aspergillus nidulans regulatory protein alcR and not fragments thereof, rejection of claims 1-4 and 9 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement has been withdrawn.

The specification at page 7, discloses the cloning of the full length alcR from an alcR cDNA containing vector. Additionally, a search in the GenBank protein data base for Aspergillus nidulans regulatory protein alcR yielded a unique result with accession No. AN8978.2. Hence, sufficient guidance is provided in the disclosures for the required structure of the Aspergillus nidulans regulatory protein alcR to satisfy the written description requirement.

In view of the withdrawn rejection, applicant's arguments are rendered moot.

Rejections/objections maintained in response to Applicants' arguments or amendments

Claim objection

Claim1 remains objected to because of the following informalities: Applicants have amended claim 1, subpart a. at line 3, to recite, "at cultivation temperature". The phrase is grammatically incorrect as an indefinite article "a" is required in front of the claimed "cultivation temperature". Appropriate correction is required.

Additionally, claims 1 and 2 are objected to because of the following informalities: Applicants have amended claim 1, subpart a. at line 2, to recite, "Aspergillus nidulans AlcR protein". The phrase is grammatically incorrect as an indefinite article "an" is required in front of the claimed "Aspergillus nidulans AlcR protein". Likewise, claim 2, at line 3 recites, "Aspergillus nidulans AlcR protein" The phrase is grammatically incorrect as a definite article "the" is required in front of the claimed "Aspergillus nidulans AlcR protein" indicating the proper antecent recited at line 2 in the same claim 1, subpart a. Appropriate correction is required.

Claim 1, at line 6, subpart b. is objected to because of the following informalities: the recitation of "obtained by amplifying said operator sites" should follow its proper antecedent in the claim, which is "linked to P_{alcA} operator sites" and not "Aspergillus nidulans AlcR protein". Appropriate correction is required.

Claim 2 is objected to because of the following informalities: at line 1, a space is required between the number 1 and the term "further". Appropriate correction is required.

Furthermore, amended claim 1 is objected to for the inclusion of the nucleotide sequences identified as SEQ ID NO:1 and SEQ ID NO:2 in parenthesis. Sequence identifiers are the best description of the claimed sequence and thus should not be recited parenthetically.

In addition, claim 1 is objected to because of the recitation of both, the SEQ No identifier and the description of the nucleotide sequence. Recitation of just the SEQ No. would obviate the redundancy.

Claims 1 is objected to because of the following informalities: abbreviations such as AlcR should be spelled out at the first encounter in the claims. Appropriate correction is required

35 USC § 112- First paragraph- Scope of enablement

Please, note that the scope of enablement has been modified in view of Applicants' remarks, in light of the guidance provided in the specification and knowledge available to one of ordinary skill in the art at the time of filing the present application, and further in view of reconsideration of search under different premises.

To the extent that claim 1 encompasses an isolated mammalian cell comprising (a) a nucleic acid, the nucleic acid encoding an acetaldehyde- responsive transcription factor AlcR transactivator, and (b) a nucleic acid comprising a promoter said promoter operatively linked to an *A. nidulans* P_{AlcA} operator sequence obtained by amplifying said operator site sequence from a P_{AlcA} containing vector with oligonucleotides of SEQ ID No. 1 and SEQ ID No. 2, the claimed invention is enabling.

The instant issue of enablement is based on the fact the instant claims embrace a genus of mammalian cell comprising the Aspergillus nidulans AlcR protein wherein the isolated mammalian host has been modified to comprise the Aspergillus nidulans AlcR protein by a genus of undefined modifications including chemical modification, modification by contact, modification by culturing cells in appropriate conditions, transfection, infection, electroporation,

etc, that may not result in the claimed nidulans AlcR protein able to exhibit *A. nidulans* AlcR-mediated transactivation in the presence of acetaldehyde so as to result in acetaldehyde - inducible expression of a target gene in a mammalian cell.

Claims 1-4 and 9 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for,

An isolated mammalian cell comprising,

(a) a nucleic acid encoding a promoter operatively linked to a nucleic acid sequence encoding an acetaldehyde- responsive transcription factor AlcR protein, and (b) a nucleic acid comprising a promoter said promoter operatively linked to an *A. nidulans* AlcR-specific P_{AlcA} operator sequence obtained by amplifying said operator site P_{AlcA} sequence from a P_{AlcA} containing vector with oligonucleotides of SEQ ID No. 1 and SEQ ID No. 2,

does not reasonably provide enablement for a mammalian host cell comprising the transcription factor AlcR protein wherein said Aspergillus nidulans AlcR protein has been introduced in the host cell by a genus of undefined modifications.

The specification as filed teaches at page 5, the *Aspergillus nidulans* AlcR protein which binds to the corresponding operator sequence as disclosed in GenBank accession No. S47331, nucleotides 30-308, in response to acetaldehyde (GenBank Accession No. S47331). Moreover, the responsive transcription factor AlcR is cloned under control of the simian virus 40 promoter by excising alcR (EcoRI/SalI) from an alcR cDNA containing vector resulting in plasmid pWW195 (p. 7, paragraph [041]) which mediates constitutive transcription expression in CHO cells. Additionally, a construct pWW192 comprising a an AlcR-dependent, acetaldehyde-inducible promoter was generated, the pWW192 was designed by cloning the AlcR-specific OP site derived from the Aspergillus nidulans wherein the operator site P_{AlcA} sequence from a P_{AlcA}

containing vector is amplified with oligonucleotides of SEQ ID No. 1 and SEQ ID No. 2. Furthermore, the specification teaches transfection of CHO-K1, BHK-21 and HeLa cells with the AlcR expression plasmid pWW195 and the corresponding promoter construct pWW192 driving expression of the reporter gene SEAP and induction of gene reporter activity in a dose-dependent manner with increasing concentrations of acetaldehyde from tobacco smoke (p. 8, paragraphs [043]-[046]). Hence, the specification merely describes one example of an expression vector encoding the *Aspergillus nidulans* AlcR protein and a nucleic acid comprising a corresponding promoter sequence introduced into the mammalian host cell by transfection wherein the AlcR protein activates the AlcR- specific P_{AlcA} operator sequence in an aldehyde inducible manner. However, the specification is silent about any factual data of any other modified mammalian cell comprising the Aspergillus nidulans AlcR protein and corresponding promoter sequence able to exhibit AlcR-mediated transactivations induced by acetaldehyde. The detail of the disclosure provided by the Applicant, in view of the prior Art, must encompass a wide area of knowledge to enable one of ordinary skill in the art at the time of the invention to practice the invention without undue experimentation. However, as it will be discussed below this undue experimentation has not been overcame by the as-filed application. Though, the specification teaches examples of CHO-K1, BHK-21 and HeLa cells transduced with nucleic acid encoding with the AlcR and the corresponding promoter construct pWW192 exhibiting *A. nidulans* AlcR-mediated transactivation in the presence of acetaldehyde, the broad aspects of any mammalian cell comprising the Aspergillus nidulans AlcR protein introduced by a genus of undefined modifications is not reasonably enable for the full scope embraced by the claims.

It was well-known in the art at the time of filing, that expression of a gene of interest requires operable linkage of the gene to a promoter that controls gene expression. One example of prior establishing that a promoter drives expression of a vector is represented by the teachings of Watson et al., (Recombinant DNA, Second Edition, 2001). Watson discloses the need of a promoter as the starting signal for RNA transcription (pp. 153-154). Therefore, it is clearly set forth in the art the required linkage of a gene to a promoter for expression of said gene. Both the specification and prior art provides sufficient guidance for one skilled in the art to make and use a mammalian cell comprising an expression vector comprising a promoter operatively linked to the nucleic acid. The specification provides sufficient guidance for one skilled in the art to make and use a mammalian cell comprising an expression vector comprising a promoter operatively linked to the nucleic acid. However, the specification fails to provide sufficient guidance or evidence for one skilled in the art to make and use a mammalian cell modified by a genus of undisclosed methods. The teachings in the specification are directed to using a promoter to express the protein encoded by the nucleic acid. Thus, to the extent the claims fail to recite distinguishing features to commensurate with the level of guidance presented, the claims are not considered enabled.

Given that no other mammalians cells are disclosed comprising the Aspergillus nidulans AlcR protein other than transduced cells, furthermore, given the unpredictability to transduce a host cells with a nucleic acid using an expression vector comprising a promoter that is not operably linked to a nucleic acid, it would have required undue experimentation to practice the instant invention to identify an enormous number of mammalian cells as broadly or generically claimed, with a resultant identification of mammalian cells comprising an Aspergillus nidulans

AlcR protein and a promoter comprising the corresponding *A. nidulans* P_{AlcA} operator sites functionally linked to said promoter specifically exhibiting *A. nidulans* AlcR-mediated transactivation in the presence of acetaldehyde, as broadly claimed.

Claim Rejections - 35 USC § 103

Claims 1, 2, 4 and 9 remain rejected under 35 USC 103 as being unpatentable over Caddick et al., US Patent No. 6,605,754, (Date of Issue August 12, 2003) in view of White (Internet article November 11, 1999, of record)

Caddick et al., discloses a chemically-inducible plant gene expression cassette comprising a first promoter operatively linked to a regulator sequence which encodes a regulator protein (e.g., responsive transcription factor) in the presence of an effective exogenous inducer (current claim 1, subpart a.) and an inducible promoter operatively linked to a target gene, the inducible promoter being activated by the regulator protein (**current claim 1, subpart b.; current claim 2**) whereby application of the inducer causes expression of the target gene (col. 4, lines 22-29). Moreover, Caddick et al., teaches that the alcA gene promoter (i.e. the alcA gene encodes alcohol dehydrogenase I) is an inducible promoter which is activated by the alcR regulator protein (e.g., responsive transcription factor) in the presence of inducer, i.e. by the protein/alcohol or protein/ketone combination (col. 2, lines 65-67 bridging to col. 3, lines 1-4). The alcA/alcR gene activation system (e.g., alcR gene encodes the alcR regulator protein) is from the fungus *Aspergillus nidulans* **(current claim 4)**. Moreover, Caddick et al., exemplifies the transient transfection of Maize protoplasts from Black Mexican Sweet cells with the gene expression cassette wherein the alcR gene product is induced by ethanol in the incubating culture media (Example 4, and col. 14 lines 35-36) and stably transformed tobacco plants wherein the

alcR gene product is induced by exogenous treatment with cyclohexanone (Example 5; col. 18, lines 55-58) (**current claim 9**). Further, Caddick et al., teaches that increase in induction of the system is dependent on higher level of expression of alcR (col. 15, lines 10-20). Furthermore, as the alcR gene product taught by Caddick, which is induced by exogenous treatment with cyclohexanone (Example 5; col. 18, lines 55-58), exhibits transcription of the linked target gene, the alcA gene promoter necessarily contains the promoter domain from a *A. nidulans* P_{AlcA} generated by using oligonucleotides OWW58 (5'-gatcgacgtcggagctaccatccaataaccc-3' SEQ ID No. 1) and OWW59 (5'-gatccctgcaggcccgctcgtttgtggctct-3', SEQ ID No. 2) as forward and reverse primers, absent evidence to the contrary.

Caddick et al., do no specifically teach transfection of mammalian cells.

However, at the time the invention was made, White MRH explicitly teaches the use of mammalian host cells to be transfected with an expression vector encoding the *Aspergillus nidulans*-derived AlcR transcription factor, which in the presence of ethanol activates transcription from promoters containing specific operator sites from *A. nidulans alcA* promoter. Moreover, White MRH discloses that vectors are introduced in mammalian cells and assay for luciferase reporter gene expression in the presence and absence of ethanol.

Therefore in view of the benefits of using the ethanol-inducible *alcR* gene expression system (e.g., time point of induction, expression level, duration of expression) in a variety of plants, as taught by Caddick et al., it would have been *prima facie* obvious for one of ordinary skill in the art to use mammalian host cells to study the ethanol-induce *alcR* gene expression system, particularly because White MRH suggest transfecting mammalian cells with expression vectors expressing the *A. nidulans*-derived AlcR transcription factor, which in the presence of

ethanol activates transcription from promoters comprising the *A. nidulans alcA* promoter. The AlcR protein activates expression from alcA by binding to specific sites in the alcA. The manipulation of previously identified DNA reporter genes and cell transformation systems is within the ordinary level of skill in the art of molecular biology. One of ordinary skill in the art would have had a reasonable expectation of success in a transforming a mammalian cell comprising a first promoter operatively linked to a regulator sequence which encodes a regulator protein (e.g., responsive transcription factor) in the presence of an effective exogenous inducer, e.g., liquid (e.g., ethanol) or gas and an inducible promoter operatively linked to a target gene of interest, the inducible promoter being activated by the regulator protein in the presence of ethanol because Caddick et al., actually exemplifies said system in a variety of plant cells and White MRH teaches the use of said system to transform mammalian host cells in regulated gene expression experiments.

Response to Applicants' arguments as they relate to rejection of claims 1, 2, 4 and 9 under 35 USC § 103

At pages 8 and 9 of Applicants' remarks filed on 03-19-2009, Applicants essentially argue that the combination of Caddick and White does not obviate the instant invention as Caddick discloses an alcR/ alcA system that is functional in plants wherein, in the presence of ethanol, acetone, butan-2-ol, cyclohexanone and others, the alcR gene product is induced and binds three specific sites in the alcA promoter. White does not complement the teachings of Caddick as the author merely suggest that ethanol is the inducer of the alcR/ alcA system; however, the system cannot be functional as ethanol is not a direct inducer of the alcR system (Flipphi) and it would require metabolization into acetaldehyde to be induction effective which

does not occur in standard mammal cells. The above arguments have been fully considered but deemed unpersuasive.

In response to applicant's argument that it would not have been obvious for one of ordinary skill in the art to combine the references as the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies i.e., "[White's] system is not functional since ethanol is not a direct inducer of the AlcR system (Flipphi et al.) and would rather require metabolization into acetaldehyde to be induction effective, which, does not occur in standard mammalian cell cultures. This is independent of whether ethanol is metabolized to acetaldehyde in liver and brain cells" is a general statement. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). This is the case here. The claims do not recite the acetaldehyde- responsive transcription factor AlcR protein taught in the specification. Hence the argument is not persuasive as they argue limitations that are not present in the claims. Furthermore, Applicants have not have not provided probative evidence to support why ethanol-utilization in a standard mammalian cell would not activate AlcR. Indeed, applicant have not provided evidence of why brain or liver cells, wherein ethanol is metabolized to acetaldehyde in cell culture, are not a standard mammalian cell (Gonthier et al., 1997, *Alcohol Clin Exp Res.* pp. 1018-23; p.1018, col. 1, last paragraph). In addition, the use of prokaryotic transcriptional regulatory elements for controlled expression of cloned genes in mammalian cells and animals was well known in the art as evidenced by the use of the *Streptomyces*-derived butyrolactone-responsive quorum-sensing systems to adjust transgene expression in mammalian cells and mice (Weber, 2003; Nucleic Acids Res. 2003 July 15;

31(14): e71) further supporting the use of the ethanol –inducible transgene expression Aspergillus nidulans AlcA/AlcR system in the White publication.

Claims 1 and 3 remain rejected under 35 USC 103 as being unpatentable over Caddick et al., US Patent No. 6,605,754, (Date of Issue August 12, 2003) in view of White (Internet article November 11, 1999, of record) as applied to claims 1, 2, 5-7 and 9 above, and further in view of Flipphi et al., (*Bichem. J.* 2002, pp. 25-31, of record).

Response to Applicants' arguments as they relate to rejection of claims 1 and 3 under 35 USC § 103

The teachings of Caddick et al., and White are outlined in the paragraph above.

Caddick et al. and White do not specifically teach induction of the alcR gene product in response to compounds being gaseous at the cultivation temperature.

However, at the time the invention was made, Flipphi et al., teaches that acetaldehyde is the sole physiological inducer of ethanol catabolism in *Aspergillus nidulans* (p. 28, col. 2 last paragraph bridging to p. 29, col. 1 first paragraph). Moreover, Flipphi et al., discloses induction of the *alc* genes by acetaldehyde at low external concentrations. Indeed, Flipphi et al., states "even at an external concentration of 32μm, this highly volatile compound could induce the expression of *alcA*" (aldehyde dehydrogenase) (p. 28, col. 1, first paragraph), implicitly indicating that acetaldehyde is a gas at culture temperature of 37C (p. 26, col. 1, paragraph 2). Note that the AlcA promoter comprises *A. nidulans*- AlcR-specific operator sequences. Additionally, Flipphi et al., discloses that in the presence of acetaldehyde, AlcR protein binds *A. nidulans* AlcR-specific P_{AlcA} operator sequence in the alcA promoter gene mediating the

induction of its own transcription and that of the structural genes alcA. Moreover, acetaldehyde is toxic at high concentrations reflected by general transcription decrease (p. 28, col. 1, paragraph 2). (**Current claim 3**).

Therefore in view of the benefits of using the ethanol-inducible *alcR* gene expression system (e.g., time point of induction, expression level, duration of expression) in a variety of plants, as taught by Caddick et al., it would have been *prima facie* obvious for one of ordinary skill in the art to use mammalian host cells to study the ethanol-induce *alcR* gene expression system, particularly because White MRH suggest transfecting mammalian cells with expression vectors expressing the *A. nidulans*-derived AlcR transcription factor, which in the presence of ethanol activates transcription from promoters the A. nidulans *alcA* promoter. Additionally, it would have been *prima facie* obvious for one of ordinary skill in the art to induce the alcR gene encoding the regulator protein alcR by incubating the host cells under culture conditions comprising non-toxic highly volatile acetaldehyde concentrations, particularly Flipphi et al., exemplifies that in the presence of acetaldehyde, AlcR protein binds *A. nidulans* AlcR-specific P_{AlcA} operator sequence in the alcA promoter gene, furthermore, acetaldehyde arising from ethanol catabolism at low concentration is the sole inductor of the alcA genes. The ALCR protein activates expression from alcA by binding to specific sites in the alcA. The manipulation of previously identified DNA reporter genes and cell transformation systems is within the ordinary level of skill in the art of molecular biology. One of ordinary skill in the art would have had a reasonable expectation of success in transforming a mammalian cell comprising a first promoter operatively linked to a sequence which encodes a ALCR protein (e.g., responsive transcription factor) in the presence of an effective exogenous inducer, e.g., liquid or gas (e.g.,

acetaldehyde) and an inducible promoter operatively linked to a target gene, the inducible promoter being activated by the regulator protein because Caddick et al., actually exemplifies said system in a variety of plant cells and White MRH teaches the use of said system in transformed mammalian host cells in regulated gene expression experiments.

Response to Applicants' arguments as they relate to rejection of claims 1 and 3 under 35 USC § 103

At page 9 of Remarks, Applicants essentially allege, "A skilled artisan knowing Flipphi et al., Caddick et al. and White would still not arrive at the claimed invention, because there is no indication or hint as to how to construct the particular mammalian cell comprising AlcR protein and the particular PalcA operator site of part b. in claim 1" . Such is not persuasive.

As stated in the paragraph above, and set forth at page 17 of the Office action filed on 04-24-2009, the alcR gene product taught by Caddick, which is induced by exogenous treatment with cyclohexanone (Example 5; col. 18, lines 55-58), exhibits transcription of the linked target gene, thus the alcA gene promoter necessarily contains the promoter domain from a *A. nidulans* P_{AlcA} generated by using oligonucleotides OWW58 (5'-gatcgacgtcggagctaccatccaataaccc-3' SEQ ID No. 1) and OWW59 (5'-gatccctgcaggcccgctcgtttgtggctct-3', SEQ ID No. 2) as forward and reverse primers, absent evidence to the contrary.

New grounds of rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 and dependent claims 2-4 and 9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, subpart b. is indefinite its reciting of an isolated mammalian cell comprising "a promoter" (at line 5, subpart b). It is unclear if the phrase "a promoter" should be interpreted to encompass a nucleic acid sequence comprising a promoter sequence or other materials of different physical structure. Therefore, the metes and bounds of "a promoter" are indefinite.

Additionally, claim 1 is indefinite its reciting "linked to P_{alcA} operator sites" in line 5, subpart b. It is unclear if the phrase "linked to P_{alcA} operator sites" should be interpreted to encompass to a P_{alcA} operator site specific sequence or materials of different physical structure. Moreover, because the phrase "P_{alcA} operator site" lacks an article, it is unclear how many P_{alcA} operator sites are operatively linked to the claimed promoter. Correction is needed to clearly define the exact sequence sites being claimed or the phrase means a nucleotide sequence comprising several AlcR-specific "P_{alcA} operator sites. Therefore, the metes and bounds of "linked to P_{alcA} operator sites" are indefinite.

Claims 2-4 and 9 are indefinite insofar as they depend from claim 1.

For the purpose of a compact prosecution, claim 1 has been interpreted as an isolated mammalian cell comprising (a) a nucleic acid, the nucleic acid encoding an acetaldehyde-responsive transcription factor AlcR transactivator, and (b) a nucleic acid comprising a promoter said promoter operatively linked to an *A. nidulans* P_{AlcA} operator sequence obtained by amplifying said operator site P_{AlcA} sequence from a P_{AlcA} containing vector with oligonucleotides of SEQ ID No. 1 and SEQ ID No. 2.

Conclusion

Claims 1-4 and 9 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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/Maria Leavitt/

Maria Leavitt, PhD
Examiner, Art Unit 1633